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(54) Title: METHOD TO PRODUCE POWDERS FOR PULMONARY OR NASAL ADMINISTRATION

(57) Abstract: A pharmaceutical formulation comprises a mixture of two or more drugs optionally together with one or more excipients, the mixture being formed by the steps of: co-crystallisation or co-precipitation of the drugs followed by micronisation or milling to produce a uniform powder having a particle size and other properties suitable for formulation for pulmonary or nasal administration.

METHOD TO PRODUCE POWDERS FOR PULMONARY OR NASAL ADMINISTRATION

This patent relates to a process for preparing combination pharmaceutical formulations for pulmonary or nasal administration. The invention also relates to formulations for such uses. The invention relates particularly to combinations of drugs used for the treatment of asthma.

Asthma can be categorised in a number of stages according to official guidelines e.g. British Thoracic Society (Thorax; 1997; 52 (suppl. 5) 51-528);Canadian Thoracic Society (Can Med Assoc. J; 1992; 147: 420 - 8);American Thoracic Society (Am J Respir Crit Care Med; 1995; 152 (suppl) 577 - 5120). In these guidelines regimens are suggested for treatment of symptoms of increasing severity. These normally start with a β_2 agonist or antimuscarinic agent and then add a steroid if the symptoms are not well enough controlled. This means that many patients have to carry two or even three inhalers with the different types of drug. Combination products have found wide commercial acceptability and a number are widely marketed. Others have been proposed in the patent literature.

Examples of β_2 agonists are salbutamol, rimiterol, bambuterol, fenoterol, pirbuterol, Isoetharine and terbutaline. Recently long acting β_2 agonists have been introduced e.g. salmeterol, eformoterol (sometimes known as formoterol). Examples of antimuscarinic agents include ipatropium bromide and oxitropium bromide. Examples of steroids include beclomethasone esters, fluticasone, budesonide and mometasone.

Examples of combination products include:-

a) Short acting β_2 agonist + antimuscarinic e.g. salbutamol + ipatropium bromide (Duovent®) fenoterol + ipatropium bromide (Combivent®).

b) Short acting β_2 agonist + corticosteroid e.g. salbutamol + beclomethasone (Ventide®).

c) Long acting β_2 agonist + corticosteroid e.g. salmeterol + fluticasone EP (Seretide®) eformoterol + budesonide EP

Such products can be used normally as aerosols, either for delivery into the lung or nose i.e. as metered dose inhalers, as dry powder inhalers usually for pulmonary use, as pressurised pump solutions for nasal administration or by the use of nebulizers.

If the formulation is a solution then there are few problems with uniformity of dosage apart from those normally associated with such devices e.g. valve design and actuator design. However, if the product is formulated as a suspension there are more problems, for example settling of the suspension in the aerosol over time, caking on the sides of the aerosol container or non uniformity of the mixture in dry powder devices. These problems are exacerbated by the fact that the powders have to be a controlled particle size to ensure delivery to the place of action. For example, in inhalation aerosols the particle size is normally controlled to a mass mean diameter of 1 - 5 microns.

The problems of non-uniformity are particularly pronounced when one of the drugs is given in a low dosage or there is some form of interaction or non compatibility between the two active ingredients in suspension.

Problems of low dose arise with ipatropium bromide because the dose can be as low as 20 micrograms per shot; eformoterol where a common dose is 12 micrograms per shot; and salmeterol where a dose of 25 micrograms is often given.

According to a first aspect of the present invention a pharmaceutical formulation comprises a mixture of two or more drugs optionally together with one or more excipients, the mixture being formed by the steps of:
co-crystallisation or co-precipitation of the drugs followed by micronisation or milling to produce a uniform powder having a particle size and other properties suitable for formulation for pulmonary or nasal administration.

Formulations of this invention may be used to ensure uniform dosing of each drug in a combination and to reduce any physical incompatibilities in suspension. The co-crystallisation or co-precipitation of the two components, and subsequent micronisation is used to produce a uniform powder suitable for formulation in pharmaceutical products for

pulmonary or nasal administration. The preferred method of manufacture may depend on the two (or more) drugs needed for the specific combination product. The following methods may be employed.

Drying of both components from a mixed solution in either an aqueous or non-aqueous solvent is preferred. Spray drying is particularly preferred.

Alternative methods include co-precipitation of both drugs from an aqueous or organic solution by addition of a less polar solvent. In this case it is necessary to ensure that both drugs are precipitated to a similar extent to ensure uniformity of drug ratio throughout the mixture.

Co-crystallisation of both drugs may be carried out from aqueous or non-aqueous solutions. Uniformity of drug ratio also needs to be ensured. An alternative method is the precipitation or crystallisation of one drug onto crystals of another. Co-crystallisation may be carried out using a super critical fluid, for example super critical carbon dioxide. Suitable apparatus is disclosed in GB-A-2322326, GB-A-2334900 and GB-A-2339165.

The particles of the combined drugs may be subsequently milled or micronised to the appropriate size e.g. 3 - 5 microns for pulmonary inhalation. However in preferred embodiments of the invention the resultant co-crystallised or co-precipitated drugs have a particle size suitable for inhalation without micronisation. Spray drying of salbutamol sulphate and ipratropium bromide from aqueous solutions is particularly advantageous as particles of 3 - 7 μm may be obtained. These may have smooth configurations suitable for use in inhalation formulators without milling or micronising.

In cases where there are stability concerns due to the intimate mixing of the two drugs causing instability of one, other ingredients e.g. antioxidants may be added.

Examples of mixed products include drugs listed in two or more of the columns below.

Salmeterol	Beclomethasone	Ipatropium Bromide
Eformoterol (Formoterol)	Fluticasone	
Salbutamol	Budesonide	Other antimuscuranic
Fenoterol	Mometasone	agents
	Other steroids	
Other short or longer acting β_2 agonists		

All drugs can be present either as bases, salts or esters as appropriate to give the best mixed product, that is a crystalline or amorphous mixture which can be milled or micronised as necessary at ambient temperatures and which is stable on storage.

Preferred mixtures of drugs include salbutamol sulphate and ipratropium bromide, and salbutamol and ipratropium bromide, eformoterol and a steroid for example beclamethasone fluticasone or budesonide. Various ratios of weights may be employed, for example but not limited to 10:1, 5:1 and 2:1.

According to a second aspect of the present invention a pharmaceutical composition includes a homogeneous mixture of salbutamol and ipratropium bromide comprising crystalline particles.

According to a third aspect of the present invention there is provided use of a pharmaceutical composition as previously described for manufacture of an aerosol for delivery into the lung or nose.

The invention is further described by means of example but not in any limitative sense.

The following drugs and mixtures were prepared by spray drying using a Buchi 190 MiniSpray Drier:

(i) salbutamol sulphate from aqueous solution: 10g of salbutamol sulphate was spray dried as a 10% w/v aqueous solution using the spray drying parameters outlined below. These parameters are similar to those used by Chawla, A. et al (International Journal of Pharmaceutics 108 (1994) 233-240).

Inlet temperature:	151-153 °C
Outlet temperature:	75-78 °C
Pump setting:	7
Air flow rate:	600-700 $1hr^{-1}$

(ii) salbutamol sulphate from ethanolic solution: 8g of salbutamol sulphate was dissolved in ethanolic solution for spray drying. The solvent used consisted of ethanol 75%, water 25%. A 0.6% w/v solution was spray dried using the following spray drying parameters:

Inlet temperature:	100-102 °C
Outlet temperature:	60-64 °C
Pump setting:	6
Air flow rate:	500 $1hr^{-1}$

(iii) salbutamol from ethanolic solution: salbutamol was spray dried from ethanol (98%) as a 2.5% w/v solution. Initially a solution containing 12.5g was spray dried. The spray drying parameters used were:

Inlet temperature:	91-94 °C
Outlet temperature:	62 °C
Pump setting:	7
Air flow rate:	700 $1hr^{-1}$

The yield was extremely low (6.9%) and material was collected only from the cyclone separator since no powder was present in the collecting vessel.

It was decided to alter the spray drying conditions and hence a lower inlet temperature, lower pump rate and decreased flow rate were used. The second attempt at spray drying Salbutamol BP from ethanolic solution (96%) consisted of 12.5g of solid spray dried as a 2.5% w/v solution. The spray drying parameters used were:

Inlet temperature:	77-79 °C
Outlet temperature:	48-50 °C
Pump setting:	5
Air flow rate:	500 lhr^{-1}

The percentage yield was approx 26%.

On this occasion powder was collected from both the collecting vessel and the cyclone.

Salbutamol BP was spray dried again under similar conditions except that the pump setting was increased to 6. 9g of powder was weighed and spray dried as a 2.5% w/v solution from ethanol (96%). The spray drying parameters used were:

Inlet temperature:	77-78 °C
Outlet temperature:	54-56 °C
Pump setting:	6
Air flow rate:	500 lhr^{-1}

The percentage yield was approx 38%.

(iv) ipratropium bromide from aqueous solution: 5g of ipratropium bromide was spray dried as a 5% w/v aqueous solution. The spray drying parameters were

Inlet temperature:	151-153 °C
Outlet temperature:	102-104 °C
Pump setting:	7
Air flow rate:	700 lhr^{-1}

(v) ipratropium bromide from ethanolic solution: ipratropium bromide was spray dried from an ethanolic solution (96%). 10g in total was spray dried as a 2.5% w/v solution. The spray drying parameters were:

Inlet temperature:	77-79 °C
Outlet temperature:	55-56 °C
Pump setting:	6
Air flow rate:	500 lhr^{-1}

Note: Practically no powder was collected from the collecting vessel. The powder appeared sticky initially. On storage under vacuum the following day the powder was observed to no longer be elastic/sticky but quite brittle and dry.

(vi) salbutamol sulphate: ipratropium bromide mixtures:

(a) 10:1 weight ratio, from aqueous solution: This co-spray dried system was prepared by weighting 10g of salbutamol sulphate and 1g of ipratropium bromide to give a total of 11g of solids. This was spray dried as a 5% w/v solution (5% total solids) using the parameters given below.

Inlet temperature:	151-153 °C
Outlet temperature:	100-102 °C
Pump setting:	7
Air flow rate:	600-700 lhr^{-1}

(b) 5:1 weight ratio, from aqueous solution: This co-spray dried system was prepared by weighing 10g of salbutamol sulphate and 2g of ipratropium bromide to give a total of 12g of solids. This was spray dried as a 5% w/v solution (5% total solids) using the parameters given below.

Inlet temperature:	151-153 °C
Outlet temperature:	99-103 °C
Pump setting:	7
Air flow rate:	700 lhr^{-1}

(c) 2:1 weight ratio, from aqueous solution: This co-spray dried system was prepared by weighing 10g of salbutamol sulphate and 5g of ipratropium bromide to give a total of 15g of solids. This was spray dried as a 5% w/v solution (5% total solids) using the parameters given below.

Inlet temperature:	151-153 °C
Outlet temperature:	99-100 °C
Pump setting:	7
Air flow rate:	600-700 lhr^{-1}

After spray drying all samples were stored in a vacuum dessicator at 4 °C.

The physical characteristics of the spray-dried compounds and mixtures were determined by xray diffraction (XRD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), Fourier transform infrared (FTI) and scanning electron microscopy (SEM).

Preparation of physical mixes

Physical mixture of salbutamol sulphate or salbutamol BP and ipratropium bromide were prepared by weighing appropriate quantities of the two materials, loading into 30g amber glass jars and mixing in a Turbula™ mixer for 5 minutes. The weights taken were: for the 10:1 weight ratio, 1g salbutamol sulphate or Salbutamol BP and 0.1g of ipratropium bromide; for the 5:1 weight ratio, 1g salbutamol sulphate or Salbutamol BP and 0.2 g of ipratropium bromide; and for the 2:1 weight ratio, 1g salbutamol sulphate or Salbutamol BP and 0.5g of ipratropium bromide.

Powder X-Ray Diffraction (XRD)

The powder X-Ray Diffractometer used was a Siemens D500 Diffractometer which consist of a DACO MP wide-range goniometer. A 1.00° dispersion slit, a 1.00° anti-scatter slit and a 0.15° receiving slit were used. The Cu anode x-ray tube was operated at 40kV and 30mA in combination with a Ni filter to give monochromatic Cu Kα X-rays. All measurements were taken from 5 to 35 on the 2 theta scale at a step size of 0.05°/second.

Differential Scanning Calorimetry (DSC)

The Differential Scanning Calorimeter used was a Mettler Toledo DSC 821^e, Mettler Toledo STAR^e software Version 5.1 with a Solaris operating system. Samples were placed in open (hermetically sealed aluminium with three vent holes) pan types under nitrogen purge. Sample weights were between 5 and 10mg. DSC experiments were run generally from 30 to 250 or 350°C (depending on degradation products) at a heating rate of 10°C/minute. Two DSC scans were obtained from each system.

Thermogravimetric Analysis (TGA)

Thermogravimetric analysis was carried out using a Mettler TG 50 linked to a Mettler MT5 balance. Data was processed using Mettler Toledo STAR^e software Version 5.1 with a Solaris operating system. Sample weights between 5 and 10mg were used and analysis carried out under nitrogen purge. The scans were generally run from 30 to 350°C at a heating rate of 10°C/minute. Two TGA scans were obtained for each system.

Scanning Electron Microscopy (SEM)

The scanning electron microscope used was the Hitachi S-3500N variable pressure scanning electron microscope. Samples were mounted and sputtered with gold spray for SEM.

Fourier Transform Infra-red Spectroscopy (FTIR)

The spectrometer used was a Perkin Elmer Paragon 1000 FTIR. KBr discs were prepared based on 1mg% sample loading. Discs were prepared by grinding the sample with KBr in an agate mortar and pestle, placing the sample in an evacuable KBr die and applying 8 tons of pressure in a Graseby Specac IR press. Two FTIR spectra were obtained for each system.

Salbutamol sulphate as supplied was a crystalline material by XRD. When spray dried from aqueous solution it was amorphous as evidenced by XRD, The amorphous material was relatively stable on heating. There was no obvious exotherm in the DSC thermogram, reflective of recrystallisation from the glass. The infrared spectrum of the spray dried sample compared to the spectrum of the original material showed a change in the OH region and no match for bands at 1546 and 1244 cm^{-1} seen in the original spectrum. There was inconsistency in the intensity of some bands between the two spectra. Small spherical particles, typical of amorphous material were observed by SEM. Particle diameters ranged from ~1μm to ~8μm. The surface of the particles was slightly dimpled.

Spray drying from ethanolic solution also resulted in an amorphous material by XRD. Again the DSC showed no obvious exotherm indicative of recrystallisation. Small spherical particles, typical of amorphous material were observed by SEM. Comparisons of SEMs showed that particles were smaller than those produced from the aqueous solution, with particle diameters less than ~3μm. The surface of the particles was slightly dimpled.

Salbutamol as supplied was a crystalline material by XRD. On spray drying from ethanolic solute, the XRD indicated the same crystalline form was present, although some peak intensity differences were evident. As the initial conditions used to spray dry the material resulted in a lower yield, the spray drying conditions were adjusted appropriately to improve the yield. A lower inlet temperature, lower pump rate (2 different settings) and decreased flow rate were used. Three spray dried samples were analysed by DSC. The major peak in the DSC occurred at the same position as the melting endotherm of salbutamol base. An exotherm, typical of the presence of an amorphous material that is

physically unstable, occurred before the melting endotherm. The position and size of this peak varied between the three samples. The energy change associated with the exotherm was lower if the DSC was performed the day after spray drying. The exotherm was also at a higher temperature. This suggests that the spray dried material contains some amorphous material which rapidly converted to the crystalline form. The infrared spectrum was a good match to the spectrum of the original material. Rough, irregular shaped particles were observed by SEM, with diameters ranging from less than 1μm to ~8 or 7μm.

Ipratropium bromide as supplied was a crystalline material by XRD. The DSC showed a major endotherm with a peak at ~237°C, which can be attributed to melting. However two further lower temperature overlapping endotherms between 80 and 120°C were also evident. TGA indicated that these lower temperature endotherms represented 3 to 4% to the total solid mass. This suggested the presence of solvent. When spray dried from aqueous solution the material remained crystalline, although the XRD pattern was somewhat different. The DSC of the spray dried material showed four endothermic events. There were two low temperature endotherms between about 85 and 120°C. The TGA did not detect any mass loss associated with these endotherms and the combined energy change associated with them was ~4J/g compared to ~122J/g for the ipratropium bromide original raw material. There was another small endothermic peak at ~208°C before the large melting endotherm. Rough, irregular shaped particles were observed by SEM, with diameters ranging from about 5 to 20μm.

When spray dried from ethanolic solution, the XRD was very similar to that of the starting material. The DSC showed two low temperature endothermic peaks as well as a higher melting endotherm. The energy changes associated with the lower temperature endotherms was smaller than that of the low temperature endotherms of the starting material (~49J/g versus 122J/g) and the TGA did not detect any mass loss associated with them. The shape of the endotherms was also somewhat different to hose of the starting material. The spray dried sample in the IR showed some changes in the OH region relative to the original material. Large crystalline particles were evidence under SEM with diameters of the order of 60μm and larger.

Salbutamol sulphate : ipratropium bromide mixtures on spray drying from aqueous solution gave amorphous materials with physicochemical characterisation (XRD, DSC) similar to the spray dried salbutamol sulphate alone. Both DSC and XRD were similar to those of spray dried salbutamol sulphate. At the three ratios studied, the ipratropium bromide appeared to be dispersed in salbutamol sulphate in an amorphous form.

When the infrared spectrum of the 10:1 systems was compared to the equivalent physical mix, the spray dried sample showed changes in appearance in the OH region. There was no match in the spray dried spectrum for bands at $1087cm^{-1}$, $1031cm^{-1}$ and $1245cm^{-1}$ and there were new bands at $1044cm^{-1}$ and $1002cm^{-1}$ in the spray dried sample.

The infrared spectrum of the 5:1 system showed some differences in the OH region. There was no match in the spray dried spectrum for bands in the mechanical mix at $1087cm^{-1}$, $1031cm^{-1}$ and $978cm^{-1}$ and there were additional bands at $1267cm^{-1}$, $1448cm^{-1}$, $1404cm^{-1}$ and $1734cm^{-1}$ in the spray dried sample.

The infrared spectrum of the 2:1 system showed some differences in the OH region and a change in intensity of some bands when compared to the equivalent physical mix. The spray dried sample showed loss of $1245cm^{-1}$, $1087cm^{-1}$ and $1030cm^{-1}$ bands and showed new bands at $1508cm^{-1}$, $1268cm^{-1}$, $1044cm^{-1}$ and $1003cm^{-1}$. Some other minor inconsistencies were apparent.

SEM showed particles from all three systems prepared to be small and spherical, typical of amorphous material.

The 10:1 sample displayed slightly dimpled particles less than $3\mu m$ in diameter.

The 5:1 systems displayed more significantly dimpled particles, with diameters less than $5\mu m$.

The 2:1 system displayed smooth spherical particles with diameters less than $7\mu m$.

The samples were tested for degradation of salbutamol. In the co-spray dried systems the level of degradants was below the acceptable limits.

CLAIMS

1. A method of preparing a pharmaceutical formulation comprising a mixture of two or more drugs optionally together with one or more excipients, the mixture being formed by the steps of:

co-crystallisation or co-precipitation of the drugs followed by micronisation or milling to produce a uniform powder having a particle size and other properties suitable for formulation for pulmonary or nasal administration.

2. A method as claimed in claim 1, wherein the mixture is formed by spray drying.

3. A method as claimed in claim 2, wherein the said mixture formed by spray drying comprises particles having a dimension below 10 μm without need for milling or micronisation.

4. A method as claimed in claims 2 or 3, wherein the mixture is formed by spray drying from aqueous solution.

5. A method as claimed in any preceding claim, wherein the drugs are salbutamol sulphate and ipratropium bromide.

6. A method as claimed in claim 1 to 4, wherein the drugs are salbutamol and ipratropium bromide.

7. A method as claimed in claims 1 to 3, wherein the drugs are a beta-agonist and a steroid.

8. A method as claimed in claim 7, wherein the beta-agonist is eformoterol.

9. A method as claimed in claim 8, wherein the steroid is selected from beclamethasone, fluticasone and budesonide.

10. A pharmaceutical formulation comprising a co-precipitation or co-crystallisation as claimed in any of claims 5 to 9, having a particle size less than 10 μm.

6. A pharmaceutical formulation comprising an intimate mixture of salbutamol sulphate and ipratropium bromide having a particle size of 3 to 7μm.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K9/16 A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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P,A	WO 99 48476 A (GLAXO) 30 September 1999 (1999-09-30) the whole document	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

...formation on patent family members

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